SUPPORT FOR THE AMENDMENTS

Claims 1-48 and 51-59 have been canceled without prejudice and in favor of new Claims 60-70. Newly added Claims 60-67 are supported by Examples 62, 76, 77, 78, 79, 80, and 81, of the originally filed specification. Further, Claim 68 is supported by Claim 51. Claim 69 is supported by Claim 51. Claim 70 is supported by Claim 52. No new matter is believed to have been added to this application by these amendments.

REMARKS

Claims 1-48 and 51-59 have been canceled without prejudice and in favor of new Claims 60-70. Favorable consideration is respectfully requested.

At the outset, Applicants thank Examiner Berch for his helpful comments during the courteous discussion of the present application held on June 17, 2003, which is summarized and expanded upon below. Further, Applicants thank Examiner Berch for indicating that the amendment above combined with the remarks below would further favorable prosecution of the present application.

The rejections of the claims under 35 U.S.C. §102(a) over JP 11158149 and §103(a) over WO 97/17329 (part of same patent family as U.S. 6,143,764) is believed to be obviated by the cancellation of these claims without prejudice. Accordingly, withdrawal of these grounds of rejection is respectfully requested.

In addition, Claims 60-70 are drawn to compounds having a chlorine atom at the 2-position of the phenyl portion attached to the urea structure, pharmaceutically acceptable salts thereof, solvates thereof, and methods of using the same. More specifically, the claimed compounds are those represented in the specification at Examples 62, 76, 77, 78, 79, 80, and

81, which find support in the priority document whose priority claim thereto was previously perfected with the Amendment and Request for Reconsideration filed November 15, 2002. Accordingly, none of the claimed compounds are anticipated by any of the references of record.

In addition, Applicants respectfully submit that there is no *prima* case of obviousness in light of any disclosures represented by JP 11158149 and/or WO 97/17329 (part of same patent family as U.S. 6,143,764). Neither of the disclosures by JP 11158149 and/or WO 97/17329 possess compounds having a degree of structural similarity to the claimed invention to be considered homologs. Further, neither disclosure provides motivation to modify the compounds disclosed therein towards the claimed compounds containing a chlorine at the 2-position of the phenyl portion attached to the claimed urea structure.

In light of the above, the compounds of JP 11158149 and/or WO 97/17329 and claimed compounds are not even homologs of each other. The Federal Circuit has defined the parameters that may be considered in determining the proper use of chemical structure as the basis for obviousness rejections under 35 U.S.C. § 103 in *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). The court cited the following examples of relationships that have given rise to a *prima facie* case of obviousness, which in turn is the standard for obviousness-type double patenting:

> triorthoesters and tetraorthoesters;
>
> stereoisomers;
>
> adjacent homologs and structural isomers; and
>
> acid and ethyl ester (*Id.*, at 1943).

In the present case, there exists no motivation to modify the compounds disclosed by JP 11158149 and/or WO 97/17329 to contain a chlorine at the 2-position of the phenyl portion attached to the claimed urea structure because JP 11158149 and/or WO 97/17329 are

silent in this regard and because the relationship between the claimed compounds and those disclosed by JP 11158149 and/or WO 97/17329 fail to satisfy any of the above-mentioned relationships to be defined as homologs by the Federal Circuit.

Further, the Office is reminded that a recent decision by the *Lee Court* indicated that the Office must provide specific motivation, hint, or suggestion, found in the references relied upon to support a *prima facia* case of obviousness and not the Applicants disclosure to supply motivation to modify compounds disclosed by JP 11158149 and/or WO 97/17329 to have the claimed chlorine at the 2-position of the phenyl portion attached to the claimed urea structure (61 USPQ2d 1430). In light of this decision, Applicants respectfully request the Office not to use the present specification to find motivation that is not present in any of the disparate disclosures of the reference discussed herein.

Even if a *prima facia* case of obviousness is maintained over the JP 11158149 and/or WO 97/17329, Applicants offer the following remarks for consideration.

The following Table A contains data extracted from the originally-filed specification at Table 2, page 195, for the Examiner's convenience and to allow the focus to be drawn thereupon the same for support of the following remarks. The data in Table 2 and reproduced, in part, below in Table A represents the inhibitory effect (in nanomolar amounts), IC50: nm, on KDR activity of the claimed compounds containing a chlorine at the 2-position of the phenyl portion attached to the claimed urea structure as well as those compounds not containing a chlorine at the 2-position of the phenyl portion attached to the urea structure. The method of ascertaining the inhibitory effect is detailed in the originally-filed specification at pages 192-194.

TABLE A

KDR inhibitory activity (IC50: nM)

	R24 = H	R24 = Cl
R29 = Ethyl	150.0 (No. 63)	3.5 (No. 76)
R29 = Propyl	150.0 (No. 64)	11.0 (No. 62)
R29 = Butyl	27.0 (No. 65)	6.0 (No. 77)
R29 = Pentyl	15.0 (No. 66)	3.4 (No. 78)
R29 = sec-Butyl	63.0 (No. 67)	18.0 (No. 79)
R29 =Allyl	24.0 (No. 68)	2.7 (No. 80)
R29 = Propynyl	64.0 (No. 69)	4.1 (No. 81)

R21, R22 = Methoxy, R23, R25, R26, R27, R28 = Hydrogen

Clearly, the data presented in Table A demonstrate that the claimed compounds containing a chlorine at the 2-position of the phenyl portion attached to the claimed urea structure are superior to those compounds that do not contain the chlorine at the 2-position of the phenyl phenyl portion attached to the urea structure, especially in their inhibitory effect on KDR activity. More specifically, Examples 62, 76, 77, 78, 79, 80, and 81, representing the claimed compounds, possess a KDR inhibitory activity of 11.0, 3.5, 6.0, 3.4, 18.0, 2.7, and 4.1 nm, respectively. Meanwhile, their counterparts that contain the similar structure, yet are absent chlorine substituent at the 2-position of the phenyl portion attached to the urea structure (i.e. 64, 63, 65, 66, 67, 68, and 69), possess a KDR inhibitory activity of 150, 150, 27, 15, 63, 24, and 64 nm, respectively. Accordingly, the claimed chlorinated compounds (i.e. Examples 62, 76, 77, 78, 79, 80, and 81) have an inhibitory effect that is 42.8, 13.6, 4.5, 4.4, 3.5, 8.9, and 15.6 times greater than that of their unchlorinated counterparts that do not contain a chlorine substituent at the 2-position of the phenyl portion attached to the claimed urea structure.

In light of the above data, the claimed compounds are clearly superior to their unchlorinated counterparts, especially in their inhibitory effect of KDR activity. Accordingly,

the claimed compounds are clearly neither disclosed nor suggested by the references discussed herein.

The rejection of the Claims 1-48 and 51-58 under 35 U.S.C. §112, second paragraph, is believed to be obviated by the cancellation of these claims. Further, Applicants added new Claim 70 which recites "said target blood vessel is at least one blood vessel that is involved in feeding at least one tissue causative of at least one disease that is selected from the group consisting of a tumor tissue, retinopathy tissue, and rheumatism tissue." Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance. Early notice to this effect is respectfully requested. Should anything further be required to place this application in condition for allowance, the Examiner is requested to contact the undersigned by telephone.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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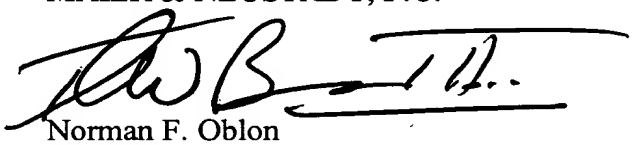

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IN THE CLAIMS

--Claims 1-48 and 51-59 are canceled.

Claims 60-70 are new.--